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ORIGINAL ARTICLE

Long-term Screening for Sleep Apnoea in Paced Patients: Preliminary Assessment of a Novel Patient Management Flowchart by Using Automatic Pacemaker Indexes and Sleep Lab Polygraphy

Ezio Aimé, MD [a*], Marina Rovida, MD [a], Danilo Contardi [b], Cristian Ricci [c], Maddalena Gaeta, MD [d], Ester Innocenti, MD [a], Jacques Cabral Tantchou-Tchoumi, MD [a]

[a]Department of Cardiology, IRCCS Policlinico San Donato, San Donato (Milan), Italy
[b]SORIN Group Italia S.r.l., Milan, Italy
[c]Universität Regensburg, Fakultät für Medizin, Institut für Epidemiologie und Präventivmedizin, Germany
[d]Unit of Biostatistic and Clinical Epidemiology, Department of Public Health and Neurosciences, University of Pavia, Italy

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Background The primary aim of this pilot study was to prospectively assess a flowchart to screen and diagnose paced patients (pts) affected by sleep apnoeas, by crosschecking indexes derived from pacemakers (minute ventilation sensor on-board) with Sleep-Lab Polygraphy (PG) outcomes. Secondarily, ''smoothed'' long-term pacemaker indexes (all the information between two consecutive follow-up visits) have been retrospectively compared vs. standard short-term pacemaker indexes (last 24 h) at each follow-up (FU) visit, to test their correlation and diagnostic concordance.

Methods Data from long-term FU of 61 paced pts were collected. At each visit, the standard short-term apnoea +hypopnoea (PM_AHI) index was retrieved from the pacemaker memory. Patients showing PM_AHI $\geq$ 30 at least once during FU were proposed to undergo a PG for diagnostic confirmation. Smoothed pacemaker (PM_SAHI) indexes were calculated by averaging the overall number of apnoeas/hypopnoeas over the period between two FU visits, and retrospectively compared with standard PM_AHI.

Results Data were available from 609 consecutive visits (overall 4.64±1.78 years FU). PM_AHI indexes were positive during FU in 40/61 pts (65.6%); 26/40 pts (65%) accepted to undergo a PG recording; Sleep-Lab confirmed positivity in 22/26 pts (84.6% positive predictive value for PM_AHI). A strong correlation (r=0.73) and a high level of concordance were found between smoothed and standard indexes (multivariate analysis, Cohen's-k and Z-score tests).

Conclusions Pacemaker-derived indexes may help in screening paced pts potentially affected by sleep apnoeas. Long-term ''smoothed'' apnoea indexes could improve the accuracy of pacemaker screening capability, even though this hypothesis must be prospectively confirmed by larger studies.

Keywords Artificial pacemaker • Sleep apnoea • Polysomnography • Apnoea and hypopnoea index • Screening • Minute ventilation sensor

*Corresponding author at: Department of Cardiology; IRCCS Policlinico San Donato, Via Morandi n. 30 - 20097 San Donato (MI). Tel.: +39 02 52774322,
Email: ezio.aime@grupposandonato.it

Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterised by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation [1]. The severity of OSAS is typically reported as the apnoea-hypopnoea index (AHI) that counts events per hour of sleep. An event can be an apnoea (complete cessation of airflow for at least 10 seconds) or a hypopnoea (>50% reduced air flow for ≥10 seconds, >30% reduction with associated decrease in oxygen saturation or arousal from sleep). Mild OSAS corresponds to an AHI 5 to 15 and moderate OSAS to AHI 15 to 30. AHI >30 events per hour represents severe sleep apnoea. OSAS is associated with an increased risk of cardiovascular complications and severe SAS is strongly associated with ventricular arrhythmias [2,3].

Polysomnography (PSG) is the gold standard for sleep disorder characterisations [4,5]. This is a complex technique that poses high demands on hospital and physician time and resources, and can be uncomfortable for patients. Alternative techniques are being developed, which need fewer sensors and in some cases rely on single parameters. However, most current alternatives tend to be less reliable than conventional PSG [6–11] although nasal pressure and heart-rate variability (HRV) have shown promise in preliminary studies [12,13].

OSAS is highly prevalent among patients indicated for cardiac pacemakers [14]. For pacemaker patients, a system was developed in 2002 (Talent 3 pacemaker, SORIN Group), that identifies sleep apnoea by combining information on resting periods (detecting body movements through an accelerometer sensor) and irregularities in respiratory cycles (from a minute ventilation sensor). A multicentre European study [15] reported a 75% sensitivity and 94% specificity with this method to identify patients with severe sleep apnoea compared with conventional PSG.

Another significant contribution comes from the DREAM study [16]: in a population of n = 40 unselected dual-chamber (75%) and single-chamber (25%) patients implanted with a pacemaker model equipped with a novel release of the sleep breathing disorders detection function (Reply 200 models,

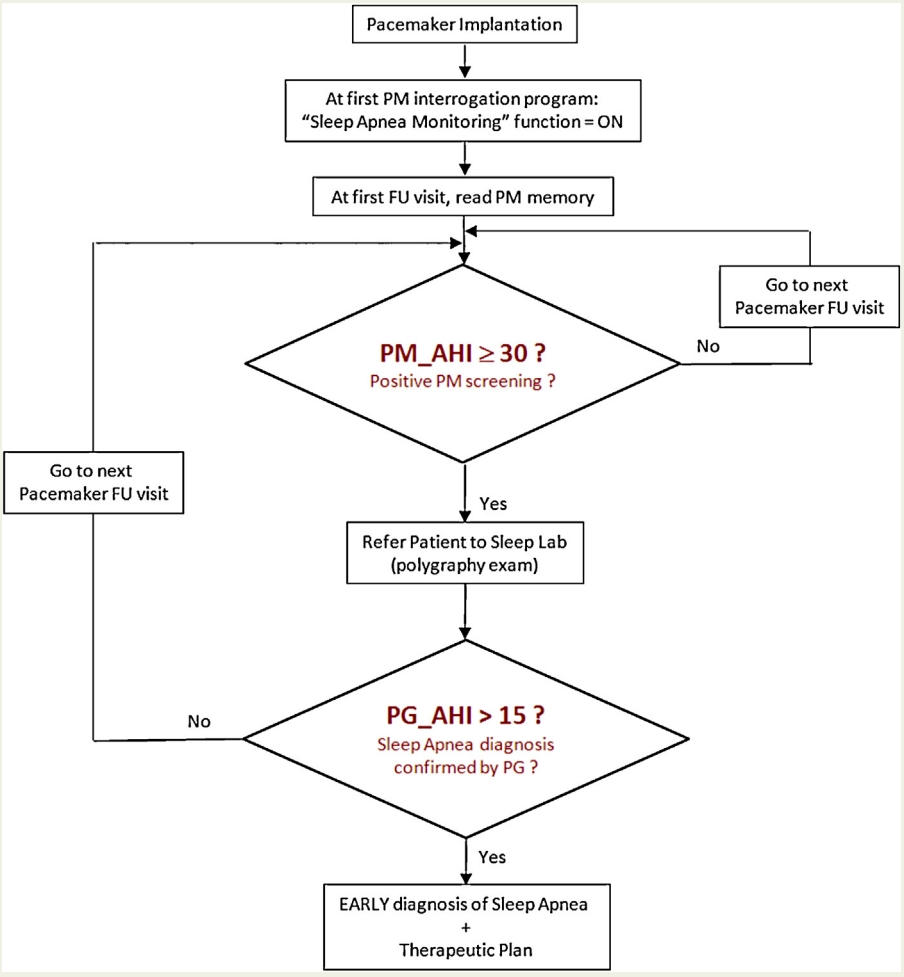

Figure 1 Flowchart of pts' management to determine the PPV of the pacemaker-derived index to screen pts at risk for sleep apnoea. PM_AHI = standard apnoea+hypopnoea index (over the last 24 h) determined by the pacemaker. PG_AHI = apnoea+hypopnoea index as determined by the polygraphy outcome (diagnostic gold-standard).

SORIN Group, Saluggia-VC, Italy), the authors found that PM-derived indexes, compared with a true polysomnography over the same night, were able to identify severe sleep apnoea positive pts with a sensitivity / specificity of 88.9% / 84.6%, respectively.

As implantable pacemakers (PMs) can provide continuous monitoring of patient conditions over extended periods of time, PM-obtained data can be used to calculate apnoea/hypopnoea indexes, either classical short-term (last 24 h) or ''smoothed'' over the entire period between two consecutive follow-up visits.

In this preliminary experience, taking into consideration the potential clinical benefit from using diagnostics from a PM equipped with dedicated software, a specific clinical approach to screen paced patients for OSAS was tested: among the entire included population, the subgroup of patients with severe OSAS according to the PM-derived short-term index (PM_AHI $\geq$ 30) was freely proposed to undergo a polygraphy (PG) exam in few neighbouring centres to confirm or not the diagnosis of OSAS.

The primary objective of this pilot experience was to assess the positive predictive value (PPV) of the PM_AHI (PM-derived short-term standard index), as determined by cross-checking with PG outcome (Fig. 1).

The secondary objective was to retrospectively evaluate the consistency of information (correlation, diagnostic concordance) between long-term ''smoothed'' (PM_SAHI) and standard short-term indexes (PM_AHI) among the entire population.

Methods

This single-centre prospective study has been entirely conducted at the IRCCS Policlinico San Donato (San Donato - Milan, Italy). A total of 61 consecutive patients (pts) were included in the database. All pts had received a Talent 3 DR PM implant and were being routinely followed-up at our institution. At the time of enrolment, none of the pts was known for a history of sleep breathing disorders or under treatment with continuous positive airway pressure (CPAP) therapy. The diagnostic feature to detect apnoea/hypopnoea events (based on data from the ventilation sensor) was activated in all devices to compute standard AHI from the information gathered over a programmable seven-hour ''sleep-window'' within the latest 24 hours, and also to record the total number of apnoea and hypopnoea events over the entire period between two consecutive FU visits. Examples of readouts from the information gathered by the pacemaker are shown in Fig. 2.

All pts gave their written agreement to the analysis of data collected during the routine PM FU visits according to local applicable regulations. Pts with a PM_AHI $\geq$ 30 as determined by the standard PM index during any of the FU visits, were freely proposed to undergo soon a PG recording, in order to confirm or not the diagnosis of OSAS. Since the data were gathered without interference with routine clinical practice, no ethics approval was required.

At each FU visit the following data were collected: 1) PM-derived apnoea + hypopnoea index (PM_AHI) calculated

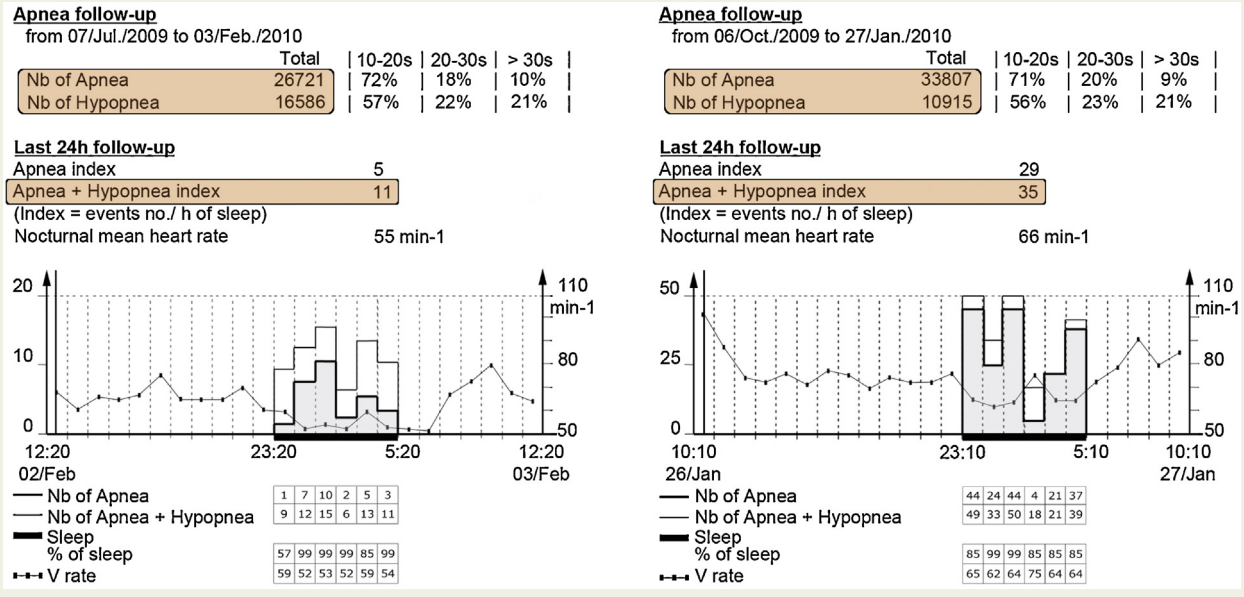

Figure 2 Two examples of follow-up (FU) outcomes, retrieved by telemetry from pacemaker memories, showing the automatic analysis of the device: a pt with low (left panel) and a pt with very high (right panel) apnoea/hypopnoea indexes. The following information was reported on a hourly basis from h 23:00 to h 6:00: number of apnoea events, number of apnoea + hypopnoea events, percentage of time asleep, mean heart rate.
In the upper parts of both panels, the overall number of apnoea (''Nb of Apnoea'') and hypopnoea (''Nb of Hypopnoea'') over the entire FU period are shown (from FU visit to FU visit).

during the last night in automatic mode during the sleep-window from h 23:00 to h 6:00; 2) time period (days) since last FU visit; 3) total number of apnoeas + hypopnoeas (Tot_AH) over this time period. Patients who underwent PG were asked to bring a copy of the PG report at the following FU visit.

A smoothed index was calculated from the recorded information, being the mean value of apnoea and hypopnoea events per hour: 'Smoothed Apnoea + Hypopnoea Index' (PM_SAHI) = (Tot_AH / Time Period) / 24. At each FU visit, PM_SAHI was calculated for the entire time period between the latest two consecutive visits.

Statistical Analysis

Primary objective: in order to compute the PPV of the PM-derived standard short-term index in identifying OSAS pts, the total number of pts identified as positive by the PG (PG_AHI $\geq$ 15, standard cut-off value for sleep apnoea positivity) was divided by the total number of pts who were identified as severely positive by the PM index and effectively underwent the PG.

Secondary objective: the distributions of all indexes are reported as means and standard deviations. The Blom rank transformation [17] was used to normalise data to calculate Pearson's correlation coefficient, 95% confidence intervals were computed by Fisher's Z Transformation [18,19].

A dedicated routine was developed using commercially available SAS-software [20] to investigate the diagnostic concordance in identifying patients at potential risk for sleep apnoea between standard and smoothed indexes. For this analysis the Cohen's κ coefficient was used. The routine adjudicates patients by means of scores calculating first the subject's Z-score, then classing subjects to dichotomous groups (by arbitrary cut-off): 'at risk' or 'not-at-risk'. Cohen's κ coefficients and confidence limits were computed and plotted by percentage of overlapping value from the mean. As a sensitivity analysis, the correlation between normalised indexes was analysed for a continuous range of detection thresholds starting from the mean and moving towards 1 standard deviation (Std-Dev) from the mean.

Furthermore a Generalised Linear Model (GLM) was applied in a multiple analysis with the normalised indexes (standard or smoothed) as response variables, and the following variables as covariates: inter-patient effect, observation time, intra-patient effect, and age. The interaction between patients and observation time was investigated by means of canonical between and within patients.

Results

The database comprised 609 FU visits from 61 pts (June 2003 to December 2009), accounting for a mean of 4.64±1.78 years FU time (median 5.06 years; minimum 1 day, maximum 7.12 years). The average time between FU visits was 170.58 ±65.14 days.

The available clinical and demographic data were gathered from hospital clinical files without interference with routine clinical practice. Consequently, only the major clinical information available at the time of PM implantation was collected. The PM implant indications were: atrio-ventricular block 25/61 (41%), sinus node disease 31/61 (51%), others 5/61 (8%). Patients were aged 71.4±10.9 years at implant time (min 41 years, max 94 years) and 50% were men. At the time of implant, none of the patients had a history of sleep breathing disorders or was under treatment with CPAP.

The value of the body mass index (BMI), available for only n = 22 pts (36%), was equal to 26.6 ± 4.1 Kg/m^2. About signs/symptoms of heart failure, none of the included patients was classified into NYHA functional class III or IV, typical finding in the real-world unselected dual-chamber PM recipients (normal or mildly reduced left ventricular ejection fraction).

Table 1 Outcomes of the sleep study (n = 26 patients).

# patient	Outcome of Polygraphy (AHI $\geq$ 15)	% OSA	% CSA	% Hypopnoeas	CPAP post-PG
1	POS	100%	0%	0%	yes
2	POS	26%	0%	74%	yes
3	POS	-	-	-	NK
4	NEG	-	-	-	no
5	POS	60%	5%	35%	NK
6	POS	95%	5%	0%	no
7	POS	100%	0%	0%	yes
8	POS	-	-	-	yes
9	POS	100%	0%	0%	yes
10	NEG	25%	0%	75%	no
11	POS	90%	10%	0%	yes
12	POS	100%	0%	0%	yes
13	NEG	-	-	-	no
14	POS	-	-	-	yes
15	NEG	100%	0%	0%	no
16	POS	33%	0%	67%	NK
17	POS	40%	0%	60%	yes
18	POS	100%	0%	0%	yes
19	POS	90%	0%	10%	yes
20	POS	60%	0%	40%	yes
21	POS	100%	0%	0%	yes
22	POS	0%	0%	100%	yes
23	POS	-	-	-	yes
24	POS	-	-	-	no
25	POS	90%	10%	0%	yes
26	POS	-	-	-	yes

OSA = Obstructive Sleep Apnoea; CSA = Central Sleep Apnoea; POS = Positive; NEG = Negative.
CPAP post-PG = evidence that the patient was under treatment after the PG examination; NK = not known, there is no clear information about CPAP treatment after PG.

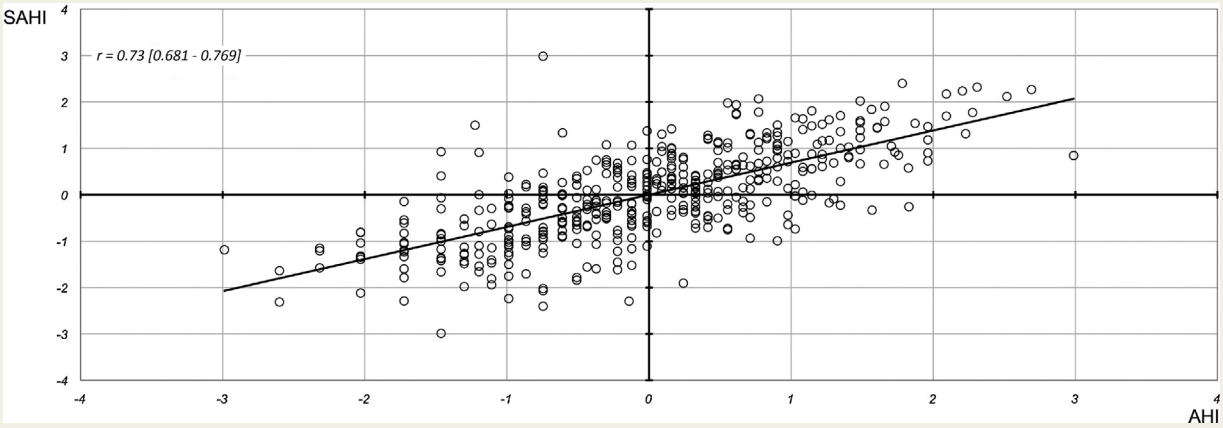

Figure 3 Pearson's correlation estimate and 95% confidence interval limits for smoothed (SAHI) vs. conventional index (AHI) derived from PM memories.

Primary Objective:

Among the entire pts' population, 40/61 pts (65.6%) were found positive by the PM (PM_AHI ≥ 30) at least once during FU: 26/40 pts (65%) effectively underwent a PG recording and 22/26 pts were confirmed as positive by the PG outcome (AHI ≥ 15, as recommended by the most recent sleep apnoea guidelines).

In Table 1 the major diagnostic (AHI ≥ 15; yes/no) and therapeutic conclusions (treated with CPAP; yes/no) for the n = 26 carried-out PGs are reported. The major finding is a clear prevalence of OSA episodes, which is consistent with anterior studies with populations of pts with preserved/mildly reduced ejection fraction. In only few pts there is a predominance of hypopnoeas.

As a consequence of the PG diagnostic outcomes, the PPV of the PM-derived standard index in identifying sleep apnoea positivity was equal to 84.6% (22/26).

Secondary Objective

The mean PM_AHI (standard short-term index) over the entire population was 23.55±14.15 (median value: 21.0), corresponding to a calculated PM_SAHI (smoothed long-term index) of 10.72±4.98 (median value: 9.52).

After normalising the distributions of indexes, the smoothed indexes highly correlated with the standard indexes; the Pearson's correlation coefficient was 0.73 for PM_SAHI vs. PM_AHI (Fig. 3).

The diagnostic concordance between the PM_SAHI and PM_AHI indexes was found to be pronounced (Fig. 4). For subjects with indexes 1 Std-Dev from the mean, Cohen's κ (diagnostic concordance PM_SAHI vs. PM_AHI) was 0.47 (k=1.0 indicates complete agreement).

The sensitivity for identification of subjects potentially at risk for sleep apnoea appeared to be greater with the smoothed indexes than with conventional indexes. With

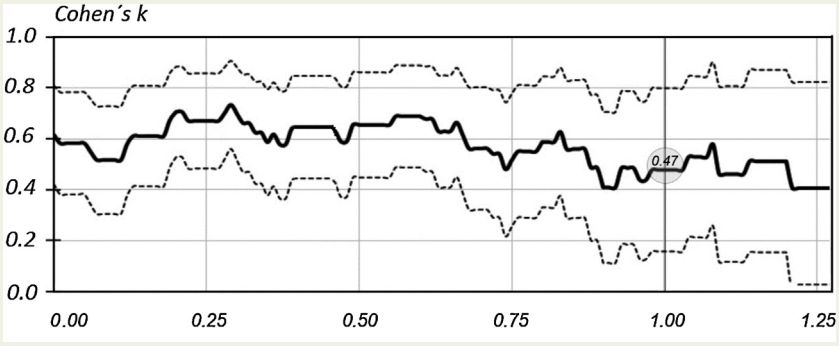

Figure 4 Cohen's κ coefficient of diagnostic concordance (ordinate) as a function of the index distribution (abscissa), smoothed (PM_SAHI) vs. standard (PM_AHI) index. The scale on the abscissa refers to deviations from the mean; 0 represents the mean value of the normalised index distribution and 1.00 represents 1 standard deviation from the mean value.

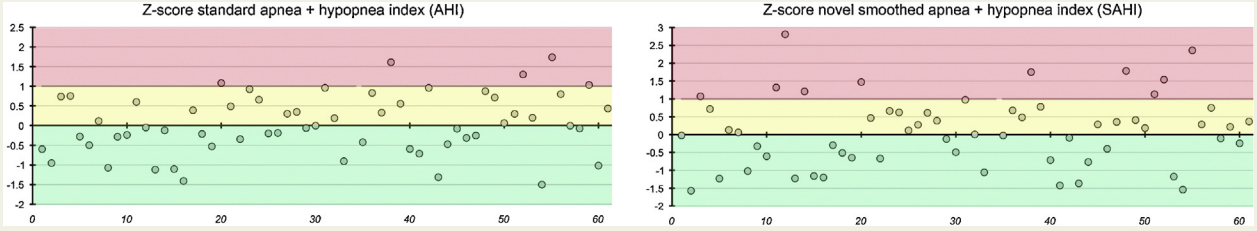

Figure 5 Z-scores method to identify subjects potentially at risk for OSAS using normalised indexes. The scale on the abscissa refers to deviations from the mean; 0 represents the mean value of the normalised index distribution and 1.00 represents 1 standard deviation from the mean value. The threshold for classification of a patient as 'at risk' for OSAS was set to mean + 1 Std-Dev. Using this threshold, more pts are classified ''at risk'' by the smoothed indexes (PM_SAHI: 10 pts) vs. standard indexes (PM_AHI: 6 pts).

the threshold to classify a patient as 'at risk' for OSAS set to the mean value + 1 Std-Dev (using normalised indexes), the smoothed indexes PM_SAHI identified 10 patients as 'at risk', compared with six pts with AHI, in the Z-score analysis (Fig. 5).

In the multiple analysis with the GLM (Table 2), the relationship between covariates and indexes was closer for PM_SAHI (R^2 = 0.872) than for PM_AHI (R^2 = 0.661), indicating that the smoothed indexes provide a better indication of potential patient risk for OSAS. There was no significant association between apnoea/hypopnoea and age with any index, although a borderline significance (p=0.069) was observed with PM_SAHI. A notable finding was a significant intra-patient variability over the observation time with both indexes (Table 2).

As an attempt to better understanding the meaning of this intra-patient variability, the distribution of the PM_AHI (mean ± standard-deviation) was calculated over all the FU visits for each of n = 60 pts (one patient excluded because of only one FU visit available). An index of variability was derived by using this formula: $\%\text{Variability} = \text{Standard Deviation}/\text{Mean}[\%\,\text{value}]$.

By using this approach - purely speculative - pts could be clustered into three groups according to the degree of % Variability (%Var):

Table 2 Outcomes from the multivariate analysis (GLM: Generalised Linear Model).

	PM_SAHI	PM_AHI
Global significance of GLM (Pr > F)	< 0.0001	< 0.0001
Between-patient	< 0.0001	< 0.0001
Observation time	0.6578	0.8796
Age	0.069	0.3471
Within-patient	0.0001	0.0232
R^2	**0.872**	**0.661**

R^2: sum of squared error components.
Covariates: Between-patient, Observation time, Age, Within-patient.

a) %Var ≤ 20%: limited variability in n = 8 patients out of 60 (13.3%); PM-derived indexes are (roughly) stable over time, thus a concordant screening information is provided;
b) 20% < %Var < 70%: moderate variability in n = 47 patients out of 60 (78.3%); in this cluster the index variability usually helps to avoid underestimation of the disease (with a single observation the risk of underestimation would be higher);
c) %Var ≥ 70%: huge variability in n = 5 patients out of 60 (8.3%); these patients, considered as outliers, are the most difficult to manage, as the interpretation of data deserve most attention to avoid complete misclassification of the screening outcome.

As there is no bibliographic support about the reproducibility of AHI values over time (no or limited data about monitoring tools able to continuously measure them over time), this interpretation must be considered on a purely speculative standpoint.

Discussion

Given the strong association between sleep disturbances and cardiovascular risk, a wider choice of uncomplicated and affordable methods to screen pts for apnoea/hypopnoea would aid in identifying individuals at risk for adverse outcomes. The data presented here show that in paced pts, the use of a monitoring system based on irregularities in resting periods and variations in respiration patterns has the potential to help in screening pts at elevated risk for OSAS.

The use of a standard apnoea+hypopnoea index, purely based upon data from the latest night prior to a FU visit, seems to be accurate enough (84.6% positive predictive value vs. polygraphy outcomes in this limited pilot experience) to implement a flowchart for pts' management (among those with an indication for permanent pacing) to provide clinicians with tools for earlier sleep apnoea diagnosis.

Furthermore, a novel long-term apnoea/hypopnoea indexes is proposed, the ''smoothed'' index, for continual assessments of sleep disturbances over long periods of time:

this smoothed index included all events captured during the period between two FU visits.

Our set of retrospective data from 609 follow-up visits over >4 years in an unselected dual-chamber paced patients indicates an excellent agreement between the novel smoothed indexes and conventional AHI indexes, as computed by the pacemaker. We found a reassuringly solid Pearson's coefficient of 0.73 for the correlation. The indexes also performed well in those subjects with values that diverged from the mean. The smoothed indexes identified >50% more patients potentially at risk for OSAS with greater sensitivity than the 24-hr indexes.

A notable finding was the significant intra-patient variability in the apnoea/hypopnoea indexes over a long follow-up period. This is particularly relevant as the majority of OSAS assessments currently rely on single analyses over the last 24 hrs prior to a follow-up visit. The smoothed indexes, based on longer measurement times, may be less sensitive to such variations. In the multivariate analysis the smoothed index PM_SAHI displayed a closer relationship to covariates than PM_AHI, indicating that smoother indexes may be more reliable than those based on single 24-hour measurements.

This preliminary pilot experience lays the foundations for prospective clinical studies comparing pacemaker data vs. gold-standard PSG defining appropriate diagnostic cut-off points to prove the usefulness of novel indexes in screening for sleep apnoea in patients with an indication for permanent dual-chamber cardiac pacing.

In the GLM there was no significant influence of age on the presence of sleep disorders as identified by the indexes. This supports what has been reported in other studies [21], although the influence of age on the incidence of sleep disorders remains a subject for debate [22]. The PM_SAHI was borderline associated with age, but given the relatively small sample size, this may well have been due to chance.

A number of alternatives to PSG have been put forward to simplify the screening of pts for sleep disturbances and to reduce the need for costly and complicated sleep centres in screening. Portable PSG monitoring systems, although cheaper than sleep centre PSG, may have unacceptably high failure rates and rates of data loss [8]. The Berlin questionnaire [6] has been suggested as a simple low-cost test for the occurrence of risk factors for OSAS, such as snoring, day-time fatigue and the presence of obesity or hypertension, and more validation studies would be welcome. Among single markers, oxygen saturation may underestimate the number of hypoxia events [11]. A more promising single marker is heart rate variability obtained by Holter recordings, for which sensitivity and specificity values of >80% have been reported [23]. More recently, nasal pressure, recorded with a modified Holter recorder, has been put forward as a relatively simple and reliable marker of sleep disorders, with particular sensitivity to awakenings [13,15].

If successfully tested in larger prospective trials on PM pts, the novel indexes may provide a simple and highly accurate alternative to Sleep Centre PSG, with the additional benefit of providing continuous data over extended periods of time. Sleep disturbances are prevalent in pts indicated for permanent pacing, with prevalence rates sometimes exceeding 50% [24]. In such pts, the system could easily be integrated together with a symptoms questionnaire and clinical investigations, in order to allow early detection of sleep breathing disorders, which could then be confirmed by dedicated sleep centre analyses.

Another interesting clinical perspective, in pts positive for sleep apnoea and subsequently treated, is that the pacing system itself can be seen as a monitor of therapeutic efficacy: the short- and long-term apnoea/hypopnoea indexes could be used to confirm whether an established therapy is effective or not in the long run.

Among weaknesses of the study should be noted: a) no precise information has been systematically gathered about medications before enrolment and during follow-up (the prescription of drugs interfering with respiratory performance could have influenced the prevalence of sleep breathing disorders); b) the retrospective design for secondary endpoint. All indexes were computed by the implantable devices and there was no comparison with indexes obtained by full-scale conventional PSG in the sleep centre. Thus, not only the smoothed indexes but also the PM_AHI indexes would need further validation. A recent small-scale comparison between pacemaker-derived and PSG sleep disturbance indexes reported no statistical differences between them [25].

The comparisons between smoothed and conventional indexes were performed after normalising the values and in order to be useful in risk assessment, all indexes would need to be correlated with the standard PSG index to make it possible to compare pts' characteristics directly. In the current study a mean PM_AHI value of 23.55 corresponded to a calculated mean PM_SAHI value of 9.52. The lower rates on the PM_SAHI are most likely an underestimate, since the smoothed indexes recorded all events between two follow-up visits, during day-time as well as night-time whereas PM_AHI refers to night-time events only. As the number of apnoeas/hypopnoeas is usually lower during daytime, the smoothed hourly indexes probably underestimate the night-time event rates. This is a weakness in the current design and long-term smoothened indexes based on night-times only might be more sensitive than the indexes used in the current analysis.

Proper cut-off points with PM_SAHI to identify mild, moderate and severe OSAS would also be needed. Similarly, the risk in pts identified with the novel indexes would need to be confirmed in further studies. As we focused on the correlations between differently calculated indexes there was no follow up for cardiovascular events and the predictive value of the PM_SAHI for cardiovascular risk needs assessment in long-term prospective studies. It would also be necessary to confirm the presence of a sub-clinical or clinical SAS identified by the smoothed indexes by a direct comparison with the PSG gold-standard diagnostic method.

Conclusion

Standard information (short-term apnoea+hypopnoea index) obtainable from dedicated pacemakers (equipped with minute ventilation sensor) can help in screening paced subjects potentially affected by OSAS, as demonstrated by prospective cross-checking with polygraphic method outcomes (pacemaker vs. polygraphy: 84.6% PPV) in this pilot experience.

Pacemaker-derived long-term indexes, gathering information from FU to FU, can be calculated at each FU visit: they've been shown to be well correlated with standard indexes and they are less sensitive to covariates.

The use of long-term indexes could improve the accuracy of the pacing device as a screening tool: this hypothesis needs to be prospectively tested by comparing pacemaker vs. polysomnographic indexes, in order to confirm the potential of this method in wider pacemaker patient populations.

Author Contributions

Data were prospectively collected by the local Pacemaker Follow-up Lab at IRCCS Policlinico San Donato, and by some of the authors (MR, EI, JCTT). Polysomnography exams have been carried out in neighbouring pneumology department/institutions. Statistical analysis was conducted at the Institut für Epidemiologie und Präventivmedizin, Germany. DC, an employee of SORIN Group Italia S.r.l., provided as technical supervision. The company had no involvement in the study funding, design or data interpretation.

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